Claim 1 and a number of the dependent claims directed to SEQ IDS NOS: 16 and 18 were rejected under 35 USC (b) as being anticipated by Wu et al, Journal of Biological Chemistry (1992) (hereinafter "Wu 1992"), or Wu et al, WO 93/04701 (hereinafter "Wu PCT"). Claim 1 and the dependent claims directed to SEQ ID NO: 12 were rejected under 35 USC 102(e) as being anticipated by Carmichael, U.S. Patent 5,728,518 (hereinafter "Carmichael"). In addition, claim 1 and many of the dependent claims were rejected under 35 USC 103(a) as being unpatentable over Korba, et al, U.S. Patent No. 5,646,262 (hereinafter "Korba") alone, and Carmichael, alone. Finally, claim 1 and many of the dependent claims were rejected pursuant to 35 U.S.C. 103(a) over various combinations with Wu 1982, WU PCT, Korba, Carmichael and Uhlmann, et al, Chemical Reviews 1990 (hereinafter "Uhlmann").

Wu 1982 and Wu PCT teach a 21 mer oligonucleotide spanning nucleotides 1903-1923 in the HBV genome. Carmichael teaches four 21 mer oligonucleotides in the HBV genome between nucleotides 1850-1910. However, none of Wu, Wu and Carmichael anticipate independent claim 1 or any of the dependent claims since none of the references teach a oligonucleotide sequence selected from the group consisting of SEQ ID NOS 7-19 and 45. Accordingly, Applicants respectfully request that the rejections pursuant to 35 U.S.C §102 over Wu and Wu, and Carmichael, be withdrawn.

Korba is directed to various oligonucleotides within the HBV genome in the region of nucleotides 1841-1908. The Office Action asserts that oligonucleotides comprising SEQ ID NOS: 7-19 and 45 would have been obvious to one of ordinary skill in the art, in light of the teaching of Korba, alone, Carmichael, alone, and Korba and/or Carmichael in combination with

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Wu 1982 and Wu PCT. According to the Office Action, one would have a reasonable expectation that additional antisense oligonucleotides targeted to the combined target sites of Korba, Carmichael, Wu 1982 and Wu PCT would have anti-HBV activity, and it would be a matter of routine experimentation to make and determine the activity of the oligonucleotides comprising SEQ ID NOS: 7-19 and 45.

Applicants respectfully submit that none of the references, either alone or in combination, teach or suggest the oligonucleotide of presently pending claim 1 wherein the oligonucleotide is selected from the group consisting of SEQ ID NOS 7-19 and 45. While each of the references teaches specific oligonucleotides having various degrees of anti-viral activity, the references as a whole also teach that that the anti-sense activity of any one particular oligonucleotide is unpredictable (*e.g.* Table 1 of Korba). The Office Action asserts that that it would have been a matter of routine experimentation to make oligonucleotides comprising SEQ ID NOS: 7-19 and 45. However, this argument, as it may apply to presently pending claim 1 directed to specific oligonucleotide sequences, is equivalent to an improper "obvious to try" argument. What is lacking from the cited art is a suggestion or motivation to make the *particular* compounds now being claimed; general motivation is insufficient. *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out."); and *Ex parte Obukowicz*, 27 U.S.P.Q.2d, 1063, 1065 (Bd. Pat. App. Int. 1992) (Prior art "that gives only general guidance and is not at all specific as to the particular form of the claimed invention and how to achieve it . . . does not make the invention obvious.").

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Except for the exact sequences that each discloses, none of references provides any guidance regarding which portions of the HBV epsilon region are critical targets for oligonucleotides having antiviral activity. Furthermore, except for the exact sequences disclosed and general information about preferred lengths of oligonucleotides, the references provide no guidance as to which of the multitude of oligonucleotide lengths and starting points within the epsilon region may be critical to an oligonucleotide having antiviral activity let alone suggest or motivate the *particular* oligonucleotides now being claimed. Therefore, the references, alone or in combination, fail to suggest the presently claimed invention. Due to the multitude of oligonucleotides that could be made, the oligonucleotides of claim 1 are clearly not a result of routine experimentation. Accordingly, Applicants respectfully submit that the presently pending claim 1 is not rendered obvious and, therefore, Applicants request that the rejection be withdrawn.

Korba, Wu 1982, Wu PCT, Carmichael and Uhlmann teach nucleotides having various modifications, compositions comprising oligonucleotides in various pharmaceutically acceptable carriers, and/or kits containing HBV oligonucleotide sequences. These references fail to compensate for the deficiencies of the primary references. Accordingly, presently pending claim 1 is not anticipated nor rendered obvious, and each of the dependent claims directed to modifications of the oligonucleotides of claim 1, compositions comprising the oligonucleotides of claim 1 in a pharmaceutically acceptable carrier, and kits comprising the oligonucleotides of claim 1, are not rendered obvious. Accordingly, Applicants respectfully request that the rejections pursuant to 35 U.S.C. §103 directed to the dependent claims for modified oligonucleotides, pharmaceutical compositions and kits be withdrawn.

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CONCLUSION

With the above amendments and remarks, Applicants respectfully submit that the application is in a condition for allowance. If the Examiner is of the opinion that a telephone conference would expedite prosecution of the application, the Examiner is encouraged to contacts Applicants' undersigned representative.

Respectfully submitted,
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APPENDIX A

Serial No: 09/901,612
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Marked-up version of amended claims

1. A synthetic oligonucleotide complementary to a portion of the [HBV RNA secondary structure in the] epsilon region of the HBV genome [comprising a nucleotide sequence] selected from the group consisting of SEQ ID NOS: 7-19 and 45, which oligonucleotide inhibits HBV replication.

8. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 7.

9. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 8.

10. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 9.

11. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 10.

12. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 11.

13. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 12.

14. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 13.

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15. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 14.

16. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 15.

17. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 16.

18 The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 17.

19. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 18.

20. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 19.

36. The synthetic oligonucleotide of claim 1 [comprising the nucleotide sequence represented by] wherein the oligonucleotide is SEQ ID NO: 45.

47. The oligonucleotide of claim 45 comprising at least one 2'-O-methyl nucleotide.

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